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IN THE

Supreme Court of the United States

ALPHAPHARM PTY., LTD. and GENPHARM, INC.,

Petitioners,

v.

TAKEDA CHEMICAL INDUSTRIES, LTD. and TAKEDA PHARMACEUTICALS NORTH AMERICA, INC.,

Respondents.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF IN OPPOSITION

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QUESTION PRESENTED

Putting aside the numerous assertions about the Federal Circuit decision on its Question Presented pages, the Petition presents the sole question: whether the Federal Circuit decision materially conflicts with this Court's decision in the *KSR* case, which the Federal Circuit fully addressed and applied to the quite different facts of this case.

CORPORATE DISCLOSURE STATEMENT

Respondent, Takeda Chemical Industries, Ltd. (now known as Takeda Pharmaceutical Company Limited) does not have a parent corporation and there is no publicly held company that owns 10% or more of its stock. Respondent, Takeda Pharmaceuticals North America, Inc., is a wholly owned subsidiary of Takeda Chemical Industries, Ltd.

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STATUTORY PROVISIONS

In addition to 35 U.S.C. § 103, this case is controlled by 35 U.S.C. § 282:

> A patent shall be presumed valid. Each claim of a patent (whether in independent, dependent, or multiple dependent form) shall be presumed valid independently of the validity of other claims. . . . The burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting such invalidity.

INTRODUCTION

Alphapharm's Petition contends that the Federal Circuit imposed a "new and onerous" requirement to establish a prima facie case of obviousness and rigidly applied the so-called "teaching, suggestion, motivation" ("TSM") test in a manner inconsistent with this Court's decision in *KSR International Co. v. Teleflex, Inc.*, 127 S. Ct. 1727 (2007). In reality, however, the Federal Circuit neither applied a rigid TSM test nor imposed any new threshold requirement; nor did it otherwise apply a standard inconsistent with *KSR*. Rather, the Federal Circuit correctly applied this Court's precedent to the particularized facts of this case to affirm the district court's extensive findings of fact under *Graham v. John Deere Co.*, 383 U.S. 1 (1966). Utilizing the *Graham* factors is precisely the approach advocated in *KSR*: the "framework for applying the statutory language of § 103," explicitly set out in *Graham*, "continue[s] to define the inquiry that controls." 127 S. Ct. at 1734.

The Petition's assertion that the Federal Circuit "rigidly" applied a TSM approach is a makeweight, attempting to grab on to *KSR*. The assertion mischaracterizes the Federal Circuit decision. The Federal Circuit evaluated and affirmed a fact-specific analysis of all the evidence – not just prior-art documents, but the testimony of experts and of Alphapharm's own representatives – as to what would have been obvious. That all-the-evidence approach, expressly following the *Graham* analysis, is just what *KSR* commends. 127 S. Ct. at 1734.

Alphapharm's real complaint is that the Federal Circuit did not give it the benefit of a *presumption* of obviousness in light of a structurally similar prior-art compound. Pet. i, 2, 12 (asserting a *rule* presuming "that structurally similar compounds . . . are prima facie obvious"). That position, however, would improperly replace the full-context *Graham-KSR* approach with a new rigid rule of obviousness, specific only to the chemical arts. Noticeably, the Petition never cites a decision of this Court for that asserted presumption. That is hardly surprising, for that approach is not just contrary to 35 U.S.C. § 282, but to the central lesson of *KSR* itself – that rigid and mandatory rules are to be avoided in favor of fact-specific inquiries into what skilled artisans would or would not have done or seen. The gravamen of the Petition thus would turn the lesson of *KSR* on its head.

Accordingly, no legal question warranting review is presented. Indeed, after *KSR* was decided, this Court denied certiorari from a quite similar decision rejecting

obviousness, as Alphapharm acknowledges. *See* Pet. 22-23 (discussing *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369 (Fed. Cir. 2006), *cert. denied*, 128 S. Ct. 146, 128 S. Ct. 288 (2007)). Not only did the two Petitions from that decision make arguments nearly identical to what Alphapharm now advances,[1] but the Respondents in *Eli Lilly* relied extensively on the Federal Circuit's decision in the present case to explain how the *Eli Lilly* decision (rendered before *KSR* was decided) was consistent with *KSR*. *See* Brief for Respondents, *Teva Pharms. USA, Inc. v. Eli Lilly & Co.*, 128 S. Ct. 146, 128 S. Ct. 288 (2007) (Nos. 06-1642, 06-1723), 2007 WL 2212737, at *16-17. Thus, this Court denied certiorari outright, rather than remand for reconsideration in light of *KSR*, even though the Federal Circuit in *Eli Lilly* had not had a chance to consider *KSR*. Here, the Federal Circuit carefully applied *KSR*, and the Petition should likewise be denied.

Ultimately, rather than raising any question of "legal significance," Alphapharm bases its Petition on an attempt to relitigate the facts it alleged, but failed to prove, below. That is not a "compelling reason" for review on a writ of certiorari. *See* SUP. CT. R. 10.

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1. *See* Brief for Petitioners-Appellants, *Teva Pharms. USA, Inc. v. Eli Lilly & Co.*, 128 S. Ct. 146 (2007) (No. 06-1642), 2007 WL 1685850, at *13-16 (challenging purported imposition of requirements to show: "motivation for one of ordinary skill in the art to" (1) "select a prior art compound as a 'lead compound,'" and (2) "modify [that] prior art compound to arrive at the patented compound."); Brief for Petitioner-Appellant, *Dr. Reddy's Labs., Ltd. v. Eli Lilly & Co.*, 128 S. Ct. 288 (2007) (No. 06-1723), 2007 WL 1850384 (same).

In any event, certiorari should be denied for the additional reason that the decision below independently rests on another ground – unexpected results that rebutted any prima facie case of obviousness, had one existed. Alphapharm never addresses or asserts error in the district court's finding that "[e]ven if Alphapharm had been able to show a prima facie case of obviousness, there is compelling and conclusive evidence that pioglitazone's non-toxicity was unexpected" (A96, A127-29),[2] or in the Federal Circuit's affirmation that the district court's "characterization of pioglitazone's unexpected properties is not clearly erroneous," and that "[c]onsequently, Takeda rebutted any presumed expectation that compound b and pioglitazone would share similar properties." A24. Alphapharm has thus failed to raise any question that could justify overturning the ultimate finding of the district court that the patent at issue is valid, or the Federal Circuit's affirmance of that finding.

STATEMENT OF THE CASE

I. Factual Background

A. The '777 Patent

Takeda owns the patent-in-suit, U.S. Patent No. 4,687,777 ("'777 patent"), which issued on August 18, 1987 (RA814-20) and will expire on January 17, 2011 (A74-75). The '777 patent shows that pioglitazone is exceptional, out of a class of hundreds of millions of

2. "A__" refers to the petition appendix in this Court. "RA__" refers to the Unified Joint Appendix in the Federal Circuit No. 06-1329, and "SA__" refers to Alphapharm's "Supplementary Appendix" filed with its Petition in this Court.

compounds, because it is both effective *and safe* for treatment of Type 2 Diabetes. A33; A68; RA814-20; *see* A12-26. Prior to the discovery of pioglitazone, other prior art compounds in this class that appeared effective were toxic. RA816(col. 1, ll. 18-40); A96; *see* A23-24. Others were safe, but ineffective. RA818(col. 1, ll. 18-40). Even Alphapharm's Rule 30(b)(6) designee, who is himself a medicinal chemist and the director of Alphapharm's Intellectual Property strategy, agreed that the data in the '777 patent established that pioglitazone is "clearly superior" to the prior art. A37; A127; *see* RA2186(17:14)-2187(19:7); *see also* RA2241(235:25-236:4); RA3177 (1238:16-23).

In July 1999, after extensive testing and clinical trials, the FDA approved pioglitazone (ACTOS®) for treatment of Type 2 Diabetes, finding it safe and effective. ACTOS® was such an important advance in medicine that it has been hugely successful, attaining annual sales in the United States of over $1.7 billion in 2003 and over $2 billion in 2004. A3; A129-131; RA4816; *see* A41. Other than pioglitazone, the FDA has only ever approved two other thiazolidinediones ("TZDs"). Rezulin®, the first FDA-approved TZD, was withdrawn due to lethal liver toxicity. A40-41; RA4824-27. Avandia® is the only other FDA-approved TZD on the market today, but studies have shown that ACTOS® is highly superior to Avandia® in its triglyceride lowering, its effects on cholesterol, its tendency to *improve* cardiovascular outcomes, and its multiple beneficial effects for atherosclerosis. A40-41; *see, e.g.*, RA1059-1063. Indeed, Alphapharm chose to pursue ACTOS® over Avandia® because of its "selective advantage." RA6644.

B. Discovery of Pioglitazone

In the mid 1970s, Takeda researchers discovered that certain TZD derivatives lowered blood glucose in diabetic mice. A2-3; A41-44; RA1076(¶25). TZDs, now known as "insulin sensitizers," appeared to have the unique potential to overcome a primary cause of Type 2 Diabetes, namely, resistance to the action of insulin. Over the next decade, Takeda studied over 2,000 separate compounds, including approximately 1,000 TZDs. A33; A41-66; RA1076-78.

Prior to the discovery of pioglitazone, many in the scientific community believed that research into "insulin sensitizers" was the wrong direction. A56; RA1614-15(¶21). Nevertheless, Takeda and its researchers forged ahead. Extensive studies on TZDs led to the synthesis of ciglitazone in February 1978, as well as many other TZDs. A44-54. As Takeda's development work progressed, however, the development team observed that ciglitazone exhibited significant toxicities, and that it was not sufficiently effective to be a successful antidiabetic. A53-54.

During its evaluation of ciglitazone, Takeda continued to search for compounds that were both safer and more effective. A53-56. Pioglitazone, internally designated AD-4833, was first synthesized on September 7, 1982. A54. Several years of additional work showed that pioglitazone was the only efficacious TZD of the hundreds tested that had no statistically significant toxicity to the heart, liver or erythrocytes (red blood cells) in standard two-week toxicity screening tests, and showed no toxicity in tests for cataract formation

(a toxicity that contributed to the discontinuation of ciglitazone's clinical trials). A23-24; A54-66; RA4638-55; RA4659-83. Takeda was excited to find that "the data of all preliminary toxicological studies so far obtained were clear" for pioglitazone. RA4692; *see* A62-66.

C. Prosecution History of The '777 Patent

The '777 patent "is directed to 'compounds which can be practically used as antidiabetic agents having a broad safety margin between pharmacological effect and toxicity or unfavorable side reactions.'" A3 (quoting RA816(col. 1, ll. 34-37)). The patent disclosure included experimental data from Takeda Official Reports A-15-34 and A-15-13, the same data Takeda had relied on in selecting pioglitazone for development. A23; A59-70; RA893-924; RA4638-55; RA4659-83.

The applicants additionally filed an Information Disclosure Statement ("IDS") that directed the Examiner's attention to several pertinent prior art references (discussed further below). The IDS expressly depicted the chemical structure of the closest prior art, designated in the '777 patent as compound b. RA856. The Examiner considered compound b, but did not reject the claims for obviousness over that compound or others. The Examiner did ask for clarification of the specification. A73-74; RA870-73. After Takeda filed a responsive Amendment and Declaration (RA876-85; RA886-92), the application was allowed, and the '777 patent issued (RA774; RA814).

In this action, Takeda relied on three claims: claim 1 covers a small group of four ethylated 2-pyridyl thiazolidinedione compounds and their pharmacologically acceptable salts; claim 2 is specifically directed to one of those compounds, pioglitazone, and its pharmacologically acceptable salts; and claim 5 covers a pharmaceutical whose active ingredient is one of the group of four compounds of claim 1 or a pharmacologically acceptable salt thereof. A3-5; A67-68; RA820(col. 10, ll. 28-65).

II. The District Court Decision

Four generic drug manufacturers, including Alphapharm and Mylan, filed Abbreviated New Drug Applications ("ANDAs") for pioglitazone. A80-81. Only Alphapharm and Mylan attacked the '777 patent as invalid for obviousness, although on different and contradictory grounds. Mylan later abandoned its obviousness claim. A81-86.

The district court took thousands of pages of direct testimony of over two dozen fact and expert witnesses by declaration and deposition transcripts, and it received thousands more pages of supporting exhibits. The court presided over eight trial days of live cross-examination, giving it the opportunity to extensively observe and examine the parties' witnesses. *See generally* A33-37; RA2267-3406. After considering all the evidence, the district court issued a 124-page opinion rejecting Alphapharm's challenge, holding that Alphapharm "failed to make even a rudimentary showing that the invention was obvious. . . ." A33.

Although Alphapharm attempts to portray the district court's "view of the law" as inconsistent with this Court's decision in *KSR*, Alphapharm wholly ignores the district court's fundamental statement and analysis of the law under *Graham*:

> The talismanic statement of the obviousness inquiry appears in *Graham*, which identifies four factual underpinnings to a determination of obviousness: (1) the scope and content of the prior art, (2) the level of ordinary skill in the art, (3) the differences between the prior art and the claimed invention, and (4) objective indicia of non-obviousness.

A91. That statement of the relevant inquiry, and the district court's analysis of the facts under it, are entirely consistent with this Court's unequivocal reaffirmation that *Graham*, "continue[s] to define the inquiry that controls." *KSR*, 127 S. Ct. at 1734.

III. The Federal Circuit's Affirmance

The Federal Circuit carefully reviewed the district court's findings under the *Graham* factors as well as the underlying record, including all of the prior art relied on by Alphapharm. The Federal Circuit held that:

> Alphapharm's challenges fail to identify grounds for reversible error. The [district] court properly considered the teachings of the prior art and made credibility determinations regarding the witnesses at trial.... Because the court's

> conclusions are not clearly erroneous and are supported by the record evidence, we find no basis to disturb them.

A25. Among the district court's findings affirmed by the Federal Circuit was the determination that "the closest prior art compound (compound b, the six-methyl) exhibited negative properties that would have directed one of ordinary skill away from that compound" – a determination of fact. A18; *see In re Harris*, 409 F.3d 1339, 1341 (Fed. Cir. 2005), *cert. denied*, 546 U.S. 1090 (2006); *In re Berg*, 320 F.3d 1310, 1312 (Fed. Cir. 2003) ("What the prior art teaches and whether it teaches away from the claimed invention are questions of fact."); *see also Graham*, 383 U.S. at 17-18 (discussing "basic factual inquiries.").

Alphapharm petitioned the Federal Circuit for panel rehearing and rehearing *en banc*, asserting fact-based arguments which are nearly identical to those advanced to this Court. The Federal Circuit rejected that petition. A170-71.

REASONS FOR DENYING THE PETITION

The Federal Circuit's decision does not conflict with the decision of any other court of appeals or, contrary to petitioners' claim, with the decision of this Court in *KSR*. Although Alphapharm cloaks its attempt to relitigate the facts in the guise of a "legal question" concerning the standard for obviousness, no such question exists. Both the district court and the Federal Circuit applied the correct legal standard, set forth in *Graham* and reaffirmed by this Court in *KSR*. *See KSR*, 127 S. Ct. at 1734. *Graham* expressly recognized that "[m]anifestly, the validity of [the patent in suit] turns on the facts," 383 U.S. at 5, and thus requires the fact-finder to consider four factual inquiries: "1) 'the scope and content of the prior art'; 2) the 'differences between the prior art and the claims'; 3) 'the level of ordinary skill in the pertinent art'; and 4) objective evidence of nonobviousness." A9-10 (quoting *KSR*, 127 S. Ct. at 1734 (quoting *Graham*, 383 U.S. at 17-18)). Here, "[i]n a thorough and well-reasoned opinion, albeit rendered before *KSR* was decided by the Supreme Court, the district court made extensive findings of fact and conclusions of law as to the four *Graham* factors." A10. The Federal Circuit then scrupulously examined the issues in light of and in accordance with *KSR* itself. *See generally* A1-30.

Alphapharm's Petition ultimately asks this Court to disregard the district court's fact-findings, as affirmed, and to find that Alphapharm "demonstrated" an entirely different set of "facts" at trial. *See, e.g.*, Pet. i, 3, 17, 20. Such a request is not an appropriate ground for certiorari. This Court has refused to second-guess

concurrent factual findings made by two courts below. *See, e.g., Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 336 U.S. 271, 275 (1949), *aff'd on reh'g*, 339 U.S. 605 (1950).

In any event, the district court, as affirmed by the Federal Circuit, had ample grounds to reject Alphapharm's version of the facts. The vast majority of Alphapharm's "facts" were supported only by the testimony of Alphapharm's expert, Dr. Mosberg, whose opinions were explicitly rejected by the district court. *See* SA93-121. The court found that, on cross-examination, Dr. Mosberg "directly contradict[ed] his direct testimony" (A109), "directly contradict[ed] Alphapharm's proposed findings of fact" (A109 n.54), presented a "recently invented analysis" which was "not supported by any intellectually rigorous analysis" (A109), and testified with "some creativity but little persuasion." A110. The court found Takeda's experts "superbly qualified" (A98), "preeminent" (A98 n.39), and "far more credible" than Dr. Mosberg (A118). That evidence, along with the other testimony and documents supporting Takeda's case, fully supported the rejection of Alphapharm's assertion of a prima facie case of obviousness.

The record also supported the finding of unexpected results that would overcome any prima facie case of obviousness – a finding that independently supports the judgment and is not even challenged by Alphapharm.

I. The Federal Circuit's Decision Is Consistent with *KSR*

Alphapharm argues that the Federal Circuit "rigidly" applied the "TSM" test. Pet. 2-3, 13-16. The Federal Circuit did no such thing. It reviewed the district court's findings under *Graham* and affirmed that "the court did not err in holding that Alphapharm failed to establish a prima facie case of obviousness." A20. In reaching this determination, the Federal Circuit analyzed its precedent relevant to prima facie obviousness for chemical compounds, and the impact of *KSR* thereon, and observed that:

> [I]n cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.

A12. That reference to "some reason" is not a "rigid" application of TSM. And it is entirely consistent with *KSR*, which "acknowledged the importance of identifying 'a reason that would have prompted a person of ordinary skill in the relevant field to combine elements in the way the new claimed invention does in an obviousness determination.'" *Id.* (quoting 127 S. Ct. at 1741). Alphapharm's contention that the Federal Circuit "required particular explicit motivation" is unsupported by the opinion's text. Pet. 12. *Compare* Pet. 3, 12, 24 *with* A1-30. As *KSR* pointed out, "[t]here is no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis," noting that TSM may provide a "helpful insight." 127 S. Ct. at 1741.

Even Alphapharm concedes that a patent challenger must point to "an apparent reason to combine the known elements in the fashion claimed." Pet. 16 (citing *KSR*, 127 S. Ct. at 1741). Alphapharm attempted, but failed, to meet that burden by claiming as *fact* that the prior art would have led one of ordinary skill in the art to select compound b as a "lead compound," and to modify it in particular ways.[3] A12-13. But, as the district court found, and the Federal Circuit confirmed: "Alphapharm failed to make that showing here." A12.

To avoid this failure of proof, and to manufacture some claimed error, Alphapharm proposes to establish a conclusive presumption of obviousness, urging this Court to hold the '777 patent claims "obvious as a matter of law." Pet. 26; *see also* Pet. 12; *id.* at i (arguing that compounds "so closely related in structure to the closest prior art . . . [are] presumed obvious under patent law."). Alphapharm's overreaching is not supported by *KSR*. In fact, *KSR* disapproved of "rigid and mandatory formulas." *Id.* at 1741. By seeking to rely on an (improper) presumption, and by ignoring relevant facts (such as toxicity, unexpected results, or secondary indicia of nonobviousness), it is Alphapharm which is asserting a "rigid and mandatory" rule, not the Federal Circuit.

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3. Alphapharm faults the Federal Circuit for "deciding the appeal as it has been argued [by Alphapharm]," asserting that "it is the province of the Federal Circuit to decide the case as the law requires." Pet. 24. That is simply another attempt by Alphapharm to disguise its failures of proof as implicating some non-existent legal issue. In any event, Alphapharm's fault-finding is necessarily at odds with the positions it advocated below. "Ordinarily, doctrines of estoppel, waiver, invited error, or the like would prohibit a party from asserting as 'error' a position that it had advocated [below]." *Key Pharms. v. Hercon Labs. Corp.*, 161 F.3d 709, 715 (Fed. Cir. 1999).

Moreover, in *KSR*, this Court expressly reaffirmed that: "[b]y direction of 35 U.S.C. § 282, an issued patent is presumed valid." 127 S. Ct. at 1737.

While a prima facie case of obviousness of an issued patent *may* be based on structural similarity between the claimed compound and the prior art, that prima facie case is never presumed – it must be *proved* by the challenger. The Federal Circuit correctly stated this rule as follows:

> Our case law concerning prima facie obviousness of structurally similar compounds is well-established. We have held that "structural similarity between claimed and prior art subject matter, proved by combining references *or otherwise*, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness." [In re] *Dillon*, 919 F.2d [688], 692 [(Fed. Cir 1990), *cert. denied*, 500 U.S. 904 (1991)]. In addition to structural similarity between the compounds, a prima facie case of obviousness also requires a showing of "adequate support in the prior art" for the change in structure. *In re Grabiak*, 769 F.2d 729, 731-32 (Fed. Cir. 1895).

A10-11 (emphasis added); *see Eli Lilly*, 471 F.3d at 1377-78. As the Federal Circuit recognized, this standard is entirely consistent with the Court's decision in *KSR*, which requires proof of facts showing "an apparent

reason to combine the known elements in the fashion claimed." *KSR*, 127 S. Ct. at 1740-41; A12.[4]

Nor was the Federal Circuit's decision inconsistent with *KSR*'s statement that "[w]hat matters is the objective reach of the claim." 127 S. Ct. at 1742. This Court's point was simply that it is a mistake to limit an obviousness analysis to asking what problem the particular inventors were working on, rather than "any need or problem known in the field of endeavor at the time of invention," to determine whether "the claim extends to what is obvious." *Id.* Nothing whatsoever in the Federal Circuit decision here makes that mistake. To the contrary, that court, like the district court, clearly focused on the perspective of the entire field, and considered all the pertinent prior art as a whole without the sorts of limitations which this Court found problematic in *KSR*. Both courts engaged in an intensive

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4. Alphapharm (Pet. 12) quotes *In re Grabiak*, 769 F.2d at 731, but even the quote does not support Alphapharm's assertion that structural similarity always triggers a presumption of obviousness: it says that "when chemical compounds have 'very close' structural similarities and similar utilities, without more, a *prima facie* case *may be* made." (emphasis added). Indeed, *Grabiak* explained that "generalization should be avoided insofar as specific chemical structures are alleged to be *prima facie* obvious one from the other," *id.* at 731, and held that the PTO failed to meet its burden of "perfecting" a prima facie case because its "argument is lacking in a critical element: *adequate support in the prior art*." *Id.* at 731-33 (emphases added). Other lower-court decisions cited by Alphapharm confirm that even in proceedings before the PTO (*i.e.*, before a patent issues and so before the presumption of *validity* in § 282 applies), a prima facie case must be "proved." *In re Dillon*, 919 F.2d at 692; *In re Mayne*, 104 F.3d 1339, 1341-42 (Fed. Cir. 1997).

factual analysis of the teachings of the prior art as a whole, including U.S. Patents Nos. 4,438,141 ("'141 patent"), 4,461,902 ("'902 patent"), and 4,340,605 ("'605 patent"),[5] in addition to Sohda II and the U.S. Patents Nos. 4,287,200 ("'200 patent") and 4,444,779 ("'779 patent"). *See, e.g.*, A14-16; A114.

Alphapharm does not suggest that some art was excluded because it was from a different field. Alphapharm accuses the Federal Circuit of "fail[ing] to perform an analysis based on the objective reach of the claim," but as support for that bald assertion, Alphapharm contends that the Federal Circuit required proof that a skilled person would select compound b as a lead compound. Pet. 14-16. Simply put, Alphapharm's argument has nothing to do with the "objective reach of the claim" language in *KSR*.

Moreover, Alphapharm's argument wrongly reads this Court's reference to the "objective reach of the claim" as supporting its impermissible "hindsight" obviousness analysis. As discussed below, Alphapharm

5. Prior to the '777 filing date, several additional patents issued to Takeda covering different classes of TZDs (*i.e.*, compounds with significantly different structures than those at issue in this case). A47-48; A53; *see* A15-16; A27; *see also* RA3155(1205:6)-RA3157(1208:3). The '141 patent, a divisional of the '200 patent, issued March 20, 1984. RA3437-48. It covered TZD compounds with a thienyl, furyl, piperidino, morphylino, or pyrrolidino moiety. *Id.* The '605 patent, also a divisional of the '200 patent, issued July 20, 1982. RA3408-18. It covered TZD compounds with a pyridyl or thiazolyl moiety. *Id.* The '902 patent, issued July 24, 1984, was not a divisional of the '200 patent. RA3427-36. It covered TZD compounds with a substituted cyclohexyl moiety. *Id.*

admitted that its obviousness analysis began with compound b because it was the closest compound structurally to pioglitazone – the patented invention. A108; RA2224(169:17-18). Yet this Court's jurisprudence consistently warns against just such backward-looking analysis. *KSR*, 127 S. Ct. 1742 ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning." (noting that *Graham*, 383 U.S. at 36 "warn[s] against a 'temptation to read into the prior art the teachings of the invention in issue' and instruct[s] courts to 'guard against slipping into the use of hindsight.'") (internal citations omitted)). *KSR's* reference to the "objective reach of the claim" did not alter that prohibition.

Finally, neither the Federal Circuit nor the district court in this case departed from this Court's carefully qualified statement that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *KSR*, 127 S. Ct. at 1732. The Federal Circuit expressly quoted that principle and simply found, as the district court had, that its factual preconditions are not met here:

> Rather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation. Significantly, the closest prior art compound (compound b, the 6-methyl) exhibited negative

> properties that would have directed one of ordinary skill in the art away from that compound.

A18; *see* A112-13. There is accordingly no legal issue warranting review.

II. The Courts Below Correctly Held, on the Facts, That Alphapharm Failed to Prove a Prima Facie Case of Obviousness

On the record, the lower courts' rejection of a prima facie case of obviousness in light of compound b (the closest prior-art compound) is correct.

A. Alphapharm presented its case based on the assertion that compound b would have been chosen by those of skill in the art at the time because the "prior art repeatedly quantified [it] as the most potent antidiabetic." Pet. 23; *see id.* at 17. The district court, affirmed by the Federal Circuit, properly rejected that assertion. Compound b was one of many possibilities; the overall prior art did not recommend it over myriad other directions, but in fact recommended structurally different compounds. A14-16 (citing A102-04, A114). Indeed the prior art as a whole taught away from that particular compound. *Id.*

The record evidence supports the district court's rejection of Alphapharm's factual contention. First the Sohda II reference gave *seven* structurally-diverse compounds (compounds 10, 12, 15, 18, 58, 73, and 99) "the highest combined efficacy score, which was a rating of 7." A106; RA1001-21; *accord* RA3144(1189:15)-

RA3146(192:17). Sohda II also identified problems with toxicity or significant adverse health effects for each and every one of those compounds (including compound b) – except for compound 99, a compound that is structurally very different from compound b. A16 (citing A106 n.51). The conclusion drawn in Sohda II was to recommend three *other* compounds entirely, based on their combination of efficacy and toxicity. As the Federal Circuit summarized:

> Significantly, Sohda II identified three specific compounds that were deemed most favorable in terms of toxicity and activity. Notably, compound b was not identified as one of the three most favorable compounds. On the contrary, compound b, was singled out as causing "considerable increases in body weight and brown fat weight."

A15; *see* A48-52; A122-23; RA1010.

Contrary to Alphapharm's assertions, neither the Fujita Declaration that Takeda submitted to the PTO (RA693-98) nor the Amendment accompanying it (RA688-92) – filed in the prosecution that led to the '200 patent – purported to identify "the best nine compounds to overcome certain prior art" (Pet. 5) or "promoted the potent antidiabetic activity of compound b" (Pet. 23). The Amendment and Fujita Declaration made the limited claim that the group of listed compounds as a whole was "far superior to [certain other] compounds which are outside the scope of the present invention [*i.e.*, compounds (i) – (iv)]. . . ." RA691. Alphapharm's own expert admitted, after studying the '200 file history,

that he "did not have an informed opinion whether a person of ordinary skill in the art with only the Fujita 1980 declaration would have made decisions about what compound to designate their lead or to guide their research." RA3136(1177:21)-RA3137(1178:21). There was simply:

> nothing in the '200 patent, or in its file history, to suggest to one of ordinary skill in the art that those nine compounds, out of hundreds of millions of compounds covered by the patent application, were the best performing compounds as antidiabetics, and hence targets for modification to seek improved properties.

A14 (citing A102-04).

When Alphapharm filed its ANDA-required "Detailed Statement," it failed to articulate any reason why one skilled in the art would select compound b (referred to as compound 58 in Sohda II) as a "lead." A102 n.47; A5732-44. And in a candid admission of impermissible hindsight, Alphapharm's first Rule 30(b)(6) witness on this topic, Dr. Rosenberg, conceded that "he only chose compound (b) from Sohda II 'because it was similar to pioglitazone.'" A108; RA2224(169:17-18). He further "admitted that there was nothing in the [Sohda II] article that would recommend that a person of ordinary skill in the art choose compound b over other compounds in the article that had the same efficacy rating." A16-17; *see* A108; RA2225(172:10-20).

Alphapharm's next Rule 30(b)(6) designee, Barry Spencer, came up with a different answer, testifying that

the person of ordinary skill would actually have chosen to investigate three separate but co-equal compounds in Sohda II, namely compounds 47 and 49, which are not pyridyl compounds, and 58 (compound b). A17; A6082(58:14-59:11). Alphapharm's trial expert, Dr. Mosberg, acknowledged that a person of ordinary skill in the art would *not* have focused particularly on compound 58, claiming instead that the person of ordinary skill in the art would have engaged in a research program designed to investigate various permutations on *all* of the 2-pyridyl, 3-pyridyl, and 4-pyridyl compounds (although with a higher priority on 2-pyridyl and 3-pyridyl). A114 n.61; RA3144(1189:4-14); A3146(1192:10-14); *see* A114-17. Finally, as the district court specifically noted, Dr. Mosberg contradicted Alphapharm's position when he testified that the statement about compound b contained in the '779 file history[6] would have led the skilled artisan *away* from that

6. The original application for the '200 patent included a large number of claims directed to various embodiments of the general formula. A45-47; *see* A14 n.4. The Examiner issued a restriction requirement, *requiring* Takeda to prosecute claims to different types of TZD compounds in separate divisional patent applications. A14; A45-48; A111. Thus, the original '200 application was divided into four separate applications, which were considered by the PTO serially, and which resulted in four separate patents: the '200 patent (RA596-605), the '605 patent (RA3408-18), the '141 patent (RA3437-3519), and the '779 patent (RA725-813), all of which are substantially identical except for the claims and the introductory numbering. A45-48; A52; A111; RA3541(¶58); RA6855-58(¶¶31-38). On March 15, 1983, Takeda filed the divisional application that issued as the '779 patent. A52; RA751-84. That application *expanded* the group of compounds previously claimed in the '605 patent. A52; A111; *see* RA6857-58(¶37), and claimed a large group of millions of compounds from the original '200 application. A15-16; A25; A52. The '779 patent issued after Takeda agreed to a Terminal Disclaimer making its expiration the same as that of the '605 patent. A52; RA798-99.

compound. A108-09; *see* A109 n.54 and accompanying text; RA3143(1187:16)-3144(1188:25); RA3148(1195:6)-3149 (1197:3).

Alphapharm complains that the district court "turned a deaf ear" to the statement in the '779 file history "that compound b had become 'especially' 'important.'" Pet. 21. That is incorrect. The district court expressly considered that material and the testimony offered by both parties about its import to the skilled artisan. As the Federal Circuit noted:

> Based on the prior art as a whole, however, the [district] court found that a person of ordinary skill in the art would not have selected compound b as a lead compound for antidiabetic treatment. Although the prosecution history of the '779 patent included the statement that characterized compound b as "especially important," ... any suggestion to select compound b was essentially negated by the disclosure of the Sodha II reference. The court reasoned that one of ordinary skill in the art would not have chosen compound b, notwithstanding the statement in the '779 patent prosecution history, "given the more exhaustive and reliable scientific analysis presented by Sodha II, which taught away from compound b, and the evidence from all of the TZD patents that Takeda filed contemporaneously with the '779 [p]atent showing that there were many promising, broad avenues for further research."

A15-16 (quoting A114).

Alphapharm's complaint that the district court "overemphasiz[ed] the side effects of compound b noted in Sohda II" (Pet. 21) is inconsistent with its own expert's testimony that the "Sohda [II] article is the key piece of prior art that the skilled artisan would look to. . . ." RA1834(¶27); *see* A98-99; *accord* RA3164(1219:1)-RA3165(1219:23). The record amply supports the finding that Sohda II "teaches away" from compound b, and the application of "common sense" supports this conclusion. *KSR*, 127 S. Ct. at 1742. Sohda II, itself, states at A1010 that "especially 57 and 58 [compound b] caused considerable increases in body weight and brown fat weight." Mylan's 30(b)(6) designee testified that the skilled artisan "would and should . . . rule . . . out" compounds 57 and 58 [compound b] because they "caus[e] considerable increases in body weight and brown fat weight, which would be on the toxicity side of the equation." RA6462(132:14)–RA6463(134:15). Alphapharm's Rule 30(b)(6) designee admitted that such a compound is "presumably not" desirable. RA2227(180:24-181:13). Alphapharm's own expert, Dr. Mosberg, agreed that "[a] medicinal chemist skilled in the art would probably read the article and accept *Sohda et al.* [sic] claim that increase in brown fat and weight gain were undesirable." RA3128(1165:10)-3129(1167:11); *see* RA3191(1259:7-12) (noting that "it would seem logical" that "weight gain in a diabetic is not a good thing.").

Contrary to Alphapharm's representation, Takeda's witnesses (Drs. Morton, Colca, and Koller) did not "admit" otherwise. *Cf.* Pet. 21-22. Dr. Morton unequivocally stated that "because of data indicating that pyridyl derivatives [compounds 57 and 58] caused such adverse health effects, people involved in or interested in this research, reading Sohda II at the time, myself included, would conclude that

this reference taught away. . . ." RA1615(¶22). Dr. Colca testified that "some people . . . were just so concerned about weight and the fact that Type II diabetics are normally heavy anyway, that we should be focusing on compounds that cause weight loss rather than weight gain, or are at least weight neutral." RA3004(982:24-983:3). Similarly, Dr. Koller testified that "reading the Sohda II text, one would eliminate compounds 57 and 58 . . . as candidates for further research as pharmaceutical compounds for the treatment of Type 2 Diabetes Mellitus at that time." RA3626(¶¶19-20).

The district court's consideration of these facts is entirely in accord with this Court's precedents. "[K]nown disadvantages in old devices which would naturally discourage the search for new inventions may be taken into account in determining obviousness." *U.S. v. Adams*, 383 U.S. 39, 52 (1966).

B. Of course, even had Alphapharm shown that an artisan seeking a medically beneficial result had focused on compound b, there was a second factual element of its case which it also needed to prove, *i.e.*, that making the changes needed to arrive at the patented compounds was a "predictable use of prior art elements according to their established functions." Pet. 16 (quoting *KSR*, 127 S. Ct. at 1740). By its own admissions, this was a necessary "threshold inquiry." *Id.* Yet the record amply demonstrates that Alphapharm failed to meet this fact-bound "threshold." Alphapharm's expert, Dr. Mosberg, admitted that "the biological activities of various substituents were 'unpredictable' based on the disclosure of Sohda II." A21 (citing A124-26); *see* RA5115-19; RA3171(1229:10-18). Dr. Mosberg agreed with Takeda's

"far more credible" (A118) expert, Dr. Danishefsky, and admitted that even where methyl-to-ethyl substitutions are made in Sohda II, the resulting biological activity was highly unpredictable. A19-23; A118-20; RA1169-79(¶¶125-48); *accord* RA3192(1261:1)-RA3195(1265:2); RA3197 (1267:13)-RA3198(1269:17). Moreover, Dr. Mosberg conceded that his espoused process of so-called "routine optimization" (upon which Alphapharm continues to rely, citing SA111-13 throughout §C of its Petition) results in success in "at most 1%" of the time. A117; RA3165(1220:11)-3168(1224:10). Additionally, Alphapharm's Rule 30(b)(6) designee, Dr. Rosenberg, admitted that "a person of ordinary skill in the art would 'look at a host of substituents, such as chlorides, halides and others, not just methyls'" (A20 (citing A118); *see* RA2224(167:7-10)), and would have to undertake an extensive research effort to determine the effect of each change (RA2236(216:15)-RA2238(222:2)). Indeed, Dr. Mosberg admitted that the skilled artisan would not be able to predict: (1) whether any particular structural modification would or would not result in a change in biological properties; (2) if there was any such change, whether the difference would be to toxicity or efficacy, or both; or (3) whether that change would be favorable or unfavorable. RA3170(1227:23)-RA3171(1229:18); *see* A125-26.

Yet in the face its own admissions, Alphapharm falsely states that it "demonstrated the reason to modify at trial." Pet. 17. But its "demonstration" is based only on the testimony of its discredited expert and otherwise unsupported attorney argument, and wholly fails to address the fact that – as its witnesses repeatedly admitted – the skilled artisan would not have had any reasonable expectation of success. *See* Pet. 17-18 (citing SA112-13). For example, Alphapharm states that "[t]he skilled artisan

would have understood that any attempt to maintain the activity of compound [b] would require ameliorating the compound's side effects by making conservative changes. . . ." Pet. 18 (citing Dr. Mosberg at SA112). But Alphapharm ignores the district court's rejection of Dr. Mosberg's theories (A20) and its contrary finding that "one skilled in the art would . . . make fairly radical changes in order to try to overcome the problems." A108.

Alphapharm's assertion that "[h]ere, the prior art repeatedly promoted substituted TZDs, including methyl and ethyl substitutions, and thus provided a reason to modify compound b with homologation and ring-walking to arrive at the claimed pioglitazone" (Pet. 16), is unsupported by any citation. In fact, that assertion is contrary to the record:

> [N]othing in the '200 and the '779 Patents, or in any other publication from Takeda, would have given one skilled in the art an expectation of success from the substitution of an ethyl for a methyl. In its patents, Takeda specifically claims a variety of substituents on identified systems. For example, the '779 Patent includes substituents on a pyridyl or thiazolyl group, noting that "[a]s examples of such substituents may be mentioned lower alkyls (e.g., methyl, ethyl, etc.), lower alkoxy groups (e.g., methoxy, ethoxy, etc.), halogens (e.g., chlorine, bromine, etc.) and hydroxyl."

A124; *see* A24-25. "There were literally *thousands* of different substituents that one of ordinary skill in the art could consider. . . ." A107 (emphasis added). Thus,

the '779 patent alone disclosed millions of possible variations. RA3541-43. And that was only one of many possible research paths. A16-17 (quoting A114). When viewed in the context of the prior art as a whole, this is a far cry from "a *finite number* of identified, *predictable* solutions." *KSR*, 127 S. Ct. at 1732 (emphases added).

The record evidence showed, the district court found, and the Federal Circuit affirmed that there was "nothing in the prior art to provide a reasonable expectation that adding a methyl group to compound b would reduce or eliminate its toxicity" or "that homologation would bring about a reasonable expectation of success." A21. Alphapharm simply failed to prove its case, does not effectively challenge the Federal Circuit's determination of no clear error, and thus has no legitimate legal issue to bring before this Court.

C. The *Eli Lilly* decision, from which this Court denied certiorari, is on point. In *Eli Lilly*, the claim at issue differed from the closest prior art by one methyl group, which is what Alphapharm contends (Pet. 17) is the case here. *See Eli Lilly*, 471 F.3d at 1377-78. Alphapharm attempts to distinguish *Eli Lilly* by asserting that "[in] *Eli Lilly*, *all* the prior art taught away from selecting an adjacent homolog as a lead compound." Pet. 23 (emphasis in original). That is a distinction without a difference – or merit. Nowhere in *Eli Lilly* did the court base its decision on a finding that "*all* of the prior art taught away." *Cf. id.* (emphasis in original). Rather in both this and the *Eli Lilly* case, the Federal Circuit affirmed factual determinations, based on the prior "art *as a whole*," that the defendant failed to prove its contention that a person of ordinary skill in

the art would have chosen the structurally closest prior art compound as a "beginning" or "lead" compound. *Eli Lilly*, 471 F.3d at 1377-78 (quoting *Eli Lilly & Co. v. Zenith Goldline Pharms.*, 364 F. Supp. 2d 820, 850 (S.D. Ind. 2005)); A15. Moreover, in *Eli Lilly*, the prior art, as a whole, taught away because it "expressed a preference" for substituents other than that claimed in the patent-in-suit. *Eli Lilly*, 471 F.3d at 1378-79 (quoting *Eli Lilly*, 364 F. Supp. 2d at 845). Here, not only did the prior art as a whole express a preference for myriad other directions, and specifically identify three compounds that are diverse from pioglitazone as "most favorable," but the prior art specifically "singled out" Alphapharm's suggested "lead" as a non-starter because a skilled artisan "would have been dissuaded from selecting a lead compound that exhibited negative effects, such as toxicity, or other adverse side effects, *especially one that causes 'considerable increases in body weight and brown fat weight.'*" A16 (emphasis added).

III. The Finding of Unexpected Results Requires Rejection of Alphapharm's Obviousness Challenge

Even if the Federal Circuit's rejection of the prima facie case were incorrect, which it is not, the judgment is correct. The Federal Circuit affirmed the district court's determination that "Takeda rebutted any presumed expectation that compound b and pioglitazone would share similar properties." A24. According to the district court:

> Even if Alphapharm had been able to show a prima facie case of obviousness, there is compelling and conclusive evidence that

> pioglitazone's non-toxicity was unexpected. Alphapharm is unable to overcome the extreme differences in the toxicity profiles between pioglitazone and prior art compound (b), whose modification it contends would have led to the discovery of pioglitazone.

A96. Alphapharm ignores both this finding and the Federal Circuit's discussion of unexpected results on pages A23-26 of the Opinion, and does not squarely challenge the Federal Circuit's ruling that "[t]he court's characterization of pioglitazone's unexpected results is not clearly erroneous." A24; *see In re Soni*, 54 F.3d 746, 749 (Fed. Cir. 1995) ("[W]hether an applicant made a showing of unexpected results is one of fact, subject to the clearly erroneous standard of review."); *see also In re Harris*, 409 F.3d at 1341. That ruling independently supports the judgment rejecting the invalidity challenge.

Alphapharm asserts that the '779 patent's prosecution history taught that "Adding Substituents to the Pyridyl Ring Would Have Resulted in Compounds with the Same *Antidiabetic Effect*," and that "making such conservative changes would not affect the compound's *antidiabetic use*." Pet. 19 (emphasis added). Alphapharm's argument focuses only on compound b's supposed efficacy, while altogether ignoring that compound's "extreme" toxicity. A159 n.105; A96-97; A127-28; *see* A24. That approach is improper. *See In re Ruschig*, 343 F.2d 965, 978 (C.C.P.A. 1965) (holding "[w]hile the evidence does show that the compound had a blood sugar level lowering property, it also disclosed that it was lethal, a fact omitted from the solicitor's argument. Very high toxicity, in our view, cancels out any

notion of anti-diabetic 'utility.'"). Instead, Alphapharm's burden was to prove by clear and convincing evidence that the invention *as a whole* would have been obvious at the time it was made to one of ordinary skill in the art. 35 U.S.C. § 103. The invention *as a whole* includes not only the structure of the compound, but *all* of its properties. As stated in the classic case of *In re Papesch*, 315 F.2d 381, 391 (C.C.P.A. 1963):

> From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing. The graphic formulae, the chemical nomenclature, the systems of classification and study such as the concepts of homology, isomerism, etc., are mere symbols by which compounds can be identified, classified, and compared. But a formula is not a compound and while it may serve in a claim to identify what is being patented, as the metes and bounds of a deed identify a plot of land, the thing that is patented is not the formula but the compound identified by it. And the patentability of the thing does not depend on the similarity of its formula to that of another compound but of the similarity of the former compound to the latter. There is no basis in law for ignoring any property in making such a comparison. An assumed similarity based on a comparison of formulae must give way to evidence that the assumption is erroneous.

Non-toxicity is a crucial pharmaceutical property. A16; A107. Alphapharm's attempt to ignore compound

b's extreme toxicity and paint compound b as exhibiting only the "most minor side effect" (Pet. 25) belies the record. Even Alphapharm's Rule 30(b)(6) designee, Dr. Rosenberg, characterized compound b as "active, but toxic." RA2231(195:15-16). As the district court found: "Compound (b) was a highly toxic compound, and nothing in the prior art would have led one skilled in the art to expect that the 5-ethyl on a 2-pyridyl ring would be non-toxic." A127-28; *see* A24; A96-97. Compound b caused statistically significant toxicity to the liver, heart and erythrocytes, in addition to causing cataracts. A23-24 (citing A59-65); RA4662. Pioglitazone was clear of adverse effects in all those tests; Takeda subjected fifty of its most promising compounds to a battery of toxicity tests, and of those pioglitazone was the only compound to emerge "clean." A66; RA4661; RA4692; *see* A23-24. As Alphapharm's 30(b)(6) designee admitted, pioglitazone is "'clearly superior' to compound (b) because of its non-toxicity."[7] A127; *see* RA2241(235:25-236:4). Alphapharm's own trial expert agreed. RA3177 (1238:16-23).

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7. Alphapharm cites *In re Coes*, 173 F.2d 1012, 1014 (C.C.P.A. 1949), for the proposition that "where the claimed invention does not exhibit 'markedly superior' properties over the prior art, the claim is obvious." Pet. 21. As an initial matter, *Coes* was distinguished in *Papesch*, 315 F.2d at 392. Moreover, the categorical pronouncement in *Coes* is a "generalization [that] should be avoided insofar as specific chemical structures are alleged to be *prima facie* obvious one from the other." *Grabiak*, 769 F.2d at 731. Fundamentally, however, Alphapharm's admission that pioglitazone is "clearly superior" to the closest prior art, in addition to the district court's finding regarding the "extreme differences" in the toxicity profiles between pioglitazone and compound b (A96; *see* A24; A127), dispatches Alphapharm's proposition, were it to apply.

These facts lead to two inescapable conclusions. First, pioglitazone was patentable even had Alphapharm succeeded in making out a prima facie case of obviousness. *See Adams*, 383 U.S. at 51. Second, this case is different from *KSR*, where there was no showing of unexpected results or secondary considerations of nonobviousness. 127 S. Ct. at 1745. Here, Takeda submitted "overwhelming," "compelling and conclusive" rebuttal evidence. *See* A95-96 (applying *Dillon*, 919 F.2d at 692-93) ("When rebuttal evidence is submitted, all evidence must be considered anew.") (citations omitted). The court considered Alphapharm's contentions of obviousness based on structural similarity (*e.g.*, A10-26 (affirming A90-132)), and the other evidence of record, including testimony of Takeda's well-qualified experts, along with Alphapharm's admissions and those of its expert. In light of all that evidence, the court concluded, and the Federal Circuit affirmed, that Takeda's "compelling and conclusive" (A95-96) evidence of unexpected results would have "rebutted any presumed expectation that compound b and pioglitazone would share similar properties." A24. Thus, Alphapharm's silence as to unexpected results renders its unfounded claims of error moot and inappropriate for review.

IV. Alphapharm's Suggestion that the Federal Circuit's Decision Will Have a Drastic Effect on "Thousands" of Cases Is Unfounded

Alphapharm tries to create the illusion of a case that warrants this Court's attention by characterizing the Federal Circuit's decision as "add[ing] an onerous new motivation requirement," and "creat[ing] a dangerous precedent for all chemical obviousness cases concerning pharmaceuticals." Pet. 24. A plain reading of the district court and Federal Circuit decisions, however, shows a simple application of *KSR*; Alphapharm's attempt to create a legal issue concerning an "onerous" motivation requirement has no basis in the court's decision.

Similarly, Alphapharm attempts to twist the court's straightforward analysis of the prior art into some new "dangerous" precedent concerning teaching away. Alphapharm contends that the decision below repudiated a previously "strict" "standard for 'teaching away.'" Pet. 24. It plainly did not. The court simply applied *KSR* and *Graham*. The district court rested its factual finding about the prior art on the very articulation of the standard for teaching away that Alphapharm accuses the Federal Circuit of improperly "abandon[ing]." *See* A92 ("Prior art teaches away from an invention 'when it suggests that the developments flowing from its disclosures are unlikely to produce the objective of the applicant's invention.'") (citations omitted). The Federal Circuit did no more than affirm that finding, made under that standard, for "[w]hat the prior art teaches and whether it teaches away from the claimed invention are questions of fact." *In re Berg*, 320 F.3d at 1312.

CONCLUSION

For the foregoing reasons, Alphapharm's Petition should be denied.

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Respectfully submitted,

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